Prasugrel: A Novel Thienopyridine Antiplatelet Agent. A Review of Preclinical and Clinical Studies and the Mechanistic Basis for Its Distinct Antiplatelet Profile

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ABSTRACT

Prasugrel (CS-747, LY640315) is a novel member of the thienopyridine class of oral antiplatelet agents that includes ticlopidine and clopidogrel. Like other thienopyridines, prasugrel is a prodrug that is inactive in vitro. Prasugrel’s distinct chemical structure permits efficient conversion to its active metabolite with a less rigorous dependence on specific cytochrome P-450 enzymes. Prasugrel is rapidly converted in vivo to an active metabolite (R-138727) that binds specifically and irreversibly to the platelet P2Y₁₂ purinergic receptor inhibiting ADP-mediated platelet activation and aggregation. Preclinical studies indicated that prasugrel is approximately 10- and 100-fold more potent at inhibiting ex vivo platelet aggregation and in vivo thrombus formation than clopidogrel and ticlopidine, respectively. Early clinical data in healthy subjects confirmed the greater platelet inhibition and consistency with prasugrel compared to clopidogrel. While the active metabolites of prasugrel and clopidogrel resulted in similar levels of platelet inhibition in vitro, the amount of each

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active metabolite generated in vivo was quite different—prasugrel (60 mg) resulting in an approximately 12-fold greater exposure to its active metabolite compared with clopidogrel (300 mg). This observation provides a mechanistic basis for the faster, greater, and more consistent inhibition of platelet aggregation observed with prasugrel. Clinical studies in patients with cardiovascular disease confirmed the potent antiplatelet effect of prasugrel compared with clopidogrel. Collectively, these phase 1/1b studies and a phase 2 study (JUMBO-TIMI 26) aided in dose selection for the recently completed phase 3 trial (TRITON-TIMI 38) in patients with acute coronary syndrome undergoing percutaneous coronary intervention.

INTRODUCTION

Platelet Involvement in Atherothrombosis and Intravascular Stenting

Platelets play a central role in the spontaneous process of atherothrombosis and in the formation of thrombi following coronary stent implantation. Platelets initially adhere to exposed subendothelial collagen, von Willebrand factor and other proteins at sites of vascular injury, atherosclerotic plaque rupture, and balloon dilatation with stenting (Fig. 1) (Badimon et al. 2002; de Gaetano 2001; Goldschmidt et al. 2002; Jackson 2007; Siller-Matula et al. 2007). Platelet activation following these interactions results in the release of adenosine diphosphate (ADP), thromboxane A2 (TXA2), and other mediators. Released ADP promotes platelet activation via the G-protein linked P2Y1 and P2Y12 purinergic receptors leading to further platelet activation, aggregation, and other platelet functions, such as platelet shape change, secretion and the development of procoagulant and pro-inflammatory activities (Cattaneo 2007; Dorsam and Kunapuli 2004; Gachet and Hechler 2005; Hollopeter et al. 2001). Activated platelets recruited to sites of coronary plaque rupture and intra-arterial stenting form aggregates that may lead to platelet-rich thrombi, vascular occlusion, tissue ischemia, and myocardial necrosis in what is collectively known as acute coronary syndrome (ACS) or stent associated thrombosis (SAT). Accordingly, agents that inhibit platelet activation and aggregation are widely used in patients with atherothrombotic disease and are routinely administered in association with percutaneous coronary intervention (PCI) with stenting (Antman et al. 2004; Braunwald et al. 2002; Massberg et al. 2003). Pharmacodynamic (PD) assessment of degree of platelet inhibition achieved during antiplatelet therapy is most commonly assessed using light transmission aggregometry (LTA). By this technique, platelet aggregation is approximated by monitoring the increase in light transmission through stirred platelet suspensions following activation and subsequent aggregation in vitro (Born and Cross 1963; Michelson et al. 2006). In the current review, reference to the PD determination of platelet aggregation is in large part based on this methodology. Inhibition of platelet aggregation (% IPA) reflects postmedication values expressed as the relative percent decrease from baseline (prior to treatment).

Clinical Importance of Thienopyridine Antiplatelet Agents

The currently approved thienopyridines include ticlopidine and clopidogrel [ticlopidine (Ticlid®) and clopidogrel (Plavix®)] both of which are prodrugs requiring in vivo metabolism each to an active metabolite that irreversibly binds to P2Y12 receptors thereby
Prasugrel inhibits ADP-mediated activities via binding of its active metabolite (R-138727) to the P2Y12 class of ADP receptor. For more detailed review of signaling pathways that accompany platelet activation (see Kahner et al. 2006). AA, arachidonic acid; ADP, adenosine diphosphate; ASA, aspirin; CYP, cytochrome P-450; TXA2, thromboxane A2.

Blocking ADP binding. This P2Y12 receptor antagonism inhibits ADP-mediated platelet activation and aggregation (Cattaneo 2007; Emmons and Taylor 2007; Quinn and Fitzgerald 1999; Sharis et al. 1998). Clopidogrel has largely replaced ticlopidine due to its once-daily dosing regimen, improved tolerability, and lowered incidence of hematologic side effects (Bertrand et al. 2000; Eshaghian et al. 2007; Plavix USPI 2006; Ticlid USPI 2001). A number of studies have demonstrated the safety and efficacy of dual antiplatelet therapy—a thienopyridine (ADP P2Y12 receptor antagonist) coadministered with aspirin—for improving clinical outcomes in patients with ACS and those undergoing PCI (Antman et al. 2004; Bertrand et al. 2000; Braunwald et al. 2002; CURE Trial Investigators 2001; Mehta et al. 2001; Smith et al. 2005; Steinhubl et al. 2002). The very high risk for early SAT over the years was shown to be substantially reduced by dual antiplatelet treatment initially with the combination of aspirin and the first thienopyridine ticlopidine (Leon et al. 1998). The CLASSICS study showed that clopidogrel plus aspirin was as effective as ticlopidine plus aspirin but with greater safety and tolerability in patients undergoing PCI with stenting (Bertrand et al. 2000). Results from larger trials (PCI-CURE and CREDO) confirmed that in patients with ACS the combination of aspirin plus clopidogrel 300 mg followed by long-term dual antiplatelet therapy with aspirin plus clopidogrel reduced major cardiovascular events compared with aspirin and placebo (Mehta et al. 2001; Steinhubl et al. 2002). However, several potential limitations of clopidogrel therapy have been reported, including variability in antiplatelet effects and a relatively slow onset of action (Angiolillo et al. 2007; Geisler and Gawaz 2007; Siller-Matula et al. 2007; O’Donoghue and Wiviott 2006; Steinhubl et al. 2002). Recently, clinical studies have linked poor antiplatelet response to clopidogrel with adverse clinical outcomes (Angiolillo et al. 2007; Gurbel and Tantry 2006).
One of the largest of these studies (EXCELSIOR, \( N = 802 \)) illustrated that residual platelet aggregation above the median following a clopidogrel 600 mg loading dose (LD) resulted in a 6.7-fold risk of major adverse cardiac events (MACE) at 30 days in patients undergoing PCI (Hochholzer et al. 2006). More recently in a similarly sized study (\( N = 804 \)), it was reported that “nonresponsiveness” to a clopidogrel 600 mg LD, as measured by LTA, was a strong independent predictor of stent thrombosis in patients receiving drug-eluting stents (Buonamici et al. 2007).

Investigational Antiplatelet Agents

Novel P2Y\(_{12}\) receptor antagonists with more potent antiplatelet effects and reduced response variability are currently in phase 3 clinical investigation, including cangrelor, AZD6140, and prasugrel. Cangrelor (AR-C69931MX) and AZD6140 (ticagrelor) are reversible, direct-acting P2Y\(_{12}\) receptor antagonists. Cangrelor is administered intravenously and AZD6140 is active orally (Husted et al. 2006; Jacobsson et al. 2002; Peters and Robbie 2004; Storey et al. 2001, 2002; Tantry et al. 2007). Phase 3 studies of all of the above agents are being conducted with doses that provide substantially higher levels of platelet inhibition than achieved with approved doses of clopidogrel. It remains to be determined whether higher levels of P2Y\(_{12}\) blockade and resulting higher levels of platelet inhibition provide increased efficacy with an acceptable safety profile, particularly with regard to bleeding.

PHARMACOLOGY OF PRASUGREL

Prasugrel (CS-747, LY640315) is a novel investigational member of the thienopyridine class of antiplatelet agents (Fig. 1) (Sugidachi et al. 2000). In preclinical and clinical studies, prasugrel has been demonstrated to be an orally active inhibitor of platelet activation and aggregation, having a faster onset of action, increased potency, and less response variability with respect to platelet inhibitory activity as compared with clopidogrel (and also preclinically as compared with ticlopidine) (Niitsu et al. 2005).

In rats, at single oral doses, prasugrel (0.3–3 mg/kg) produced dose-related IPA; it was approximately 10- and 100-fold more potent than clopidogrel or ticlopidine on a mg/kg basis, respectively (Sugidachi et al. 2000). The platelet inhibitory effect of prasugrel (1–10 mg/kg) in rats was evident as early as 30 min, achieving more than 80% inhibition after a single oral administration. These platelet inhibitory effects lasted for >3 days, reflecting the irreversible interaction between prasugrel’s active metabolite and its target receptor (Niitsu et al. 2005). The antithrombotic effects of prasugrel were also investigated and compared with clopidogrel and ticlopidine in a rat arteriovenous shunt thrombosis model. Consistent with platelet inhibitory activity, prasugrel (0.1–3 mg/kg), on a mg/kg basis, had approximately 10 and 100 times greater antithrombotic activity compared with clopidogrel and ticlopidine, respectively (Sugidachi et al. 2000; Niitsu et al. 2005). Rat studies demonstrated more efficient generation of the prasugrel active metabolite as compared with clopidogrel, leading to greater \textit{ex vivo} antiplatelet potency (Fig. 2) (Sugidachi et al. 2007). Combined administration of prasugrel and aspirin in rats produced greater inhibition of both platelet aggregation and thrombus formation compared with either drug alone consistent with the alternate pathways these agents inhibit (Fig. 1) (Niitsu et al. 2005).
**FIG. 2.** (A) *Ex vivo* effects of prasugrel and clopidogrel on platelet aggregation induced by 3 μM ADP in rats. (B) Plasma concentrations of active metabolites of prasugrel and clopidogrel after oral administration of each agent in rats. Note that clopidogrel doses are 10-fold higher than prasugrel doses. All data = mean ± SEM, n = 5. AM, active metabolite. Modified and reproduced with permission from Blackwell Publishing (Sugidachi et al. 2007).

*In vitro* rat and subsequent human platelet studies demonstrated that prasugrel’s active metabolite (R-138727) inhibited platelet aggregation in a concentration-dependent manner and was relatively specific to ADP compared with collagen and thrombin (Kurihara et al. 2005; Niitsu et al. 2005; Sugidachi et al 2000, 2001). In addition to inhibiting platelet aggregation, the active metabolite also inhibits other consequences of platelet activation, such as GPIIb/IIIa activation, platelet-leukocyte aggregate formation, platelet procoagulant activity, and inhibition of platelet thromboinflammatory markers (Frelinger et al. 2005, 2006a,b; Judge et al. 2007).
Prasugrel Active Metabolite Generation, Pharmacokinetics, and Pharmacodynamics

As with clopidogrel and ticlopidine, prasugrel is a prodrug and must be converted to an active metabolite that mediates platelet inhibition. The first step in the generation of prasugrel's active metabolite is the formation of the thiolactone, R-95913 (Fig. 1), which is formed following the rapid hydrolysis of prasugrel by esterases, such as those found in the intestine, liver, and plasma. R-95913 is further metabolized via oxidation by intestinal and hepatic cytochrome P-450 (CYP) enzymes in a single step that leads to ring opening and formation of the SH-containing active metabolite R-138727. This active metabolite is detected in human plasma within 15 min of dosing and reaches maximum plasma concentration at approximately 30 min (Brandt et al. 2007a; Farid et al. 2007a,b). Renal excretion is the major route for elimination of prasugrel metabolites in humans (Farid et al. 2007a). In vitro studies indicate the active metabolite generation occurs primarily by CYP3A and CYP2B6 with lesser contributions by CYP2C9 and CYP2C19 (Rehmel et al. 2006). Importantly, in vitro studies indicate that R-95913 and R-138727 would not be expected to substantially inhibit CYP1A2-, CYP2C9-, CYP2C19-, CYP2D6-, or CYP3A-mediated in vivo metabolism of coadministered drugs (Rehmel et al. 2006). In contrast to prasugrel, approximately 85% of clopidogrel is rapidly degraded by esterases to an inactive carboxylic acid metabolite (Plavix USPI 2006). Conversion of the remaining clopidogrel to its active metabolite is a 2-step cytochrome P-450-dependent process mediated by CYP3A, CYP2B6, CYP1A2, CYP2C9, and CYP2C19 (Lin et al. 1999; Kurihara et al. 2005; Savi et al. 2000). More recent studies have confirmed the roles of CYP3A and CYP2C19 in conversion of clopidogrel to its active metabolite and the consequences of their inhibition or dysfunction (Brandt et al. 2007b; Farid et al. 2007b; Hulot et al. 2006; Suh et al. 2006).

A difference between prasugrel's and clopidogrel's metabolic profiles and consequent PD responses was evident in a recent coadministration study with ketoconazole, a potent CYP3A inhibitor. While ketoconazole significantly reduced the maximum concentration ($C_{\text{max}}$) of R-138727, the overall extent of exposure, the area under the time–concentration curve (AUC) was not significantly affected, nor were prasugrel's platelet inhibitory effects. However, CYP3A inhibition by ketoconazole significantly reduced both the $C_{\text{max}}$ and AUC for clopidogrel's active metabolite and its platelet inhibitory effects. These data suggest that for prasugrel if CYP3A is inhibited, alternative CYPs, namely CYP2B6, 2C19, and 2C9, are capable of forming the active metabolite R-138727, whereas clopidogrel would appear to be more dependent on CYP3A (Farid et al. 2007b). This may be of clinical importance since certain medications and dietary components have been shown to alter CYP3A activity.

CLINICAL STUDIES

Phase 1 Healthy Subject Studies

Three early phase 1 studies confirmed observations made in preclinical animal models that prasugrel was approximately 10 times more potent than clopidogrel for both LD and maintenance dose (MD) regimens (Asai et al. 2006; Jakubowski et al. 2006; Matsushima et al. 2006). Notably, in a double-blind clopidogrel comparison study, the majority of the prasugrel 10- and 20-mg–treated subjects demonstrated a consistent level of IPA (range...
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of 42–71%) while approximately 50% of the clopidogrel-treated (75 mg) subjects showed little or widely variable inhibition (Jakubowski et al. 2006).

A crossover study in healthy, aspirin-free subjects demonstrated significantly higher IPA from 30 min to 24 h after administration of a prasugrel 60 mg LD compared with a clopidogrel 300 mg LD (Fig. 3A) with the maximum IPA of prasugrel of 78.8 ± 9.2%, approximately double that of clopidogrel (35.0 ± 24.5%). Of note, all individuals who responded poorly to clopidogrel achieved robust platelet inhibition when crossed over to prasugrel (Fig. 3B) (Brandt et al. 2007a). These data have been further confirmed by an integrated analysis from three clinical pharmacology studies comparing clopidogrel and prasugrel using an objective Bayesian methodology for classifying clopidogrel PD poor responders (Weerakkody et al. 2007). The crossover study of Brandt et al. 2007a also demonstrated higher levels of prasugrel’s active metabolite, further confirming the mechanistic basis for the faster onset, as well as greater and more consistent platelet inhibitory effects with prasugrel compared to clopidogrel. As reported, in this study the Cmax and AUC for prasugrel’s active metabolite were approximately 14- and 12-fold greater than for clopidogrel’s active metabolite (Brandt et al. 2007a; Payne et al. 2005) (Fig. 4). On a dose-adjusted basis, this represents an approximately 60-fold greater active metabolite exposure following prasugrel.

As discussed earlier, thienopyridines are commonly used in combination with aspirin in clinical practice in patients with ACS and those with ACS undergoing PCI (CURE Trial Investigators 2001; Mehta et al. 2001). A dose-ranging study was performed in healthy subjects comparing the effects of prasugrel and clopidogrel coadministered with aspirin. Prasugrel in combination with aspirin inhibited ADP-induced platelet aggregation in a dose-dependent manner. The levels of IPA at 2 h post-LD for prasugrel 40 and 60 mg LDs were 55% and 60%, respectively, and 36% for the clopidogrel 300 mg LD, a difference that was maintained through 24 h. In addition, prasugrel was found to provide a greater platelet inhibitory effect in combination with aspirin not only for ADP-induced but also for collagen- and TRAP-induced platelet aggregation (Jakubowski et al. 2007).

Overall Phase 1 Safety

In healthy subject phase 1 studies to date, prasugrel has been well tolerated at single doses up to 80 mg and repeated doses of up to 15 mg daily for as long as 28 days. As with clopidogrel, the most frequently reported adverse events in healthy subjects were hematoma and/or minor bleeding predominantly related to venipunctures. In addition, these clinical pharmacology studies have demonstrated no evidence of hepatic or central nervous system toxicity, neutropenia, thrombocytopenia, or QTc prolongation (Asai et al. 2006; Brandt et al. 2007a; Jakubowski et al. 2006; Jakubowski et al. 2007; Matsushima et al. 2006).

Patients Studies

The first patient study was a phase 1b dose-ranging study of prasugrel and clopidogrel for 4 weeks in 101 patients with stable coronary artery disease on a background of aspirin.
FIG. 3. (A) Inhibition of ADP-induced platelet aggregation for prasugrel (60 mg) and clopidogrel (300 mg) loading doses. (B) Individual levels of IPA after clopidogrel 300 mg or prasugrel 60 mg 24 hours after loading dose. Subjects were administered clopidogrel and prasugrel in a crossover fashion separated by a 14-day washout period. Reproduced with permission from Elsevier Inc. (Brandt et al. 2007a).
**FIG. 4.** Plasma active metabolite concentrations following prasugrel 60 mg LD and clopidogrel 300 mg LD. $C_{\text{max}}$, maximal concentration; AUC, area under the time-concentration curve; $T_{\text{max}}$, time of maximal concentration; *coefficient of variation, $T_{\text{max}}$ expressed as median (**range). Derived from Brandt et al. 2007a and Payne et al. 2005.

(clopidogrel 300 mg LD/75 mg MD or a prasugrel 40 or 60 mg LD/5, 7.5, 10, or 15 mg MD) (Jernberg et al. 2006). At 2 h, the earliest time point studied, prasugrel 40 and 60 mg LDs produced significantly higher IPA than the clopidogrel 300 mg MD. PD nonresponders were defined as an IPA $< 20\%$ in response to 20 $\mu$M ADP (Fig. 5A). Significantly, fewer nonresponders were identified with the prasugrel 40 and 60 mg LDs and 10 and 15 mg MDs compared with the clopidogrel-dosing regimen. Concerning safety, the number of bruising and minor bleeding adverse events was similar in the prasugrel 5, 7.5, and 10 mg groups compared with clopidogrel 75 mg. Although a nonsignificant increase in minor bruising and bleeding events was observed in the prasugrel 15 mg MD group, in a post-hoc analysis there was no correlation between the level of IPA and bleeding adverse events (Jernberg et al. 2006).

**JUMBO-TIMI 26** was a phase 2, dose ranging, safety trial of prasugrel versus clopidogrel in 904 patients undergoing elective or urgent PCI. After diagnostic catheterization, patients were randomized to either clopidogrel 300 mg LD/75 mg MD or prasugrel as a low-dose regimen (40 mg LD/7.5 mg MD), an intermediate-dose regimen (60 mg LD/10 mg MD), or a high-dose regimen (60 mg LD/15 mg MD). Treatment with the MD of the study drug was continued once daily for 29 to 34 days with coadministration of enteric-coated aspirin 325 mg daily. No significant differences were observed for the 30-day primary safety endpoint of non-CABG-related TIMI major and minor bleeding
between prasugrel and clopidogrel ($P = 0.590$). In addition, no significant differences were observed for prasugrel compared with clopidogrel in the composite safety endpoint of non-CABG-related TIMI major, minor, and minimal bleeding events (Fig. 6A). However, more TIMI minimal bleeding events were detected in the high-dose prasugrel group (3.6%) compared with the low-dose (2.0%), intermediate-dose group (1.5%), and the clopidogrel group (2.4%). Regarding secondary efficacy endpoints, there was a nonsignificant reduction in the 30-day composite of cardiovascular death, myocardial infarction (MI), stroke, recurrent...
myocardial ischemia requiring hospitalization or clinical target vessel thrombosis in the combined prasugrel groups compared with the clopidogrel group. This difference was primarily driven by decreases in MI and urgent reintervention (Fig. 6B) (Wiviott et al. 2005).

The phase 1 and 2 safety and PD data served as the basis for the phase 3 dose selection and further investigation of prasugrel in ACS patients undergoing PCI. This trial,
TRITON-TIMI 38 was a randomized, double-blind, double-dummy, parallel group, multi-center, multinational clinical trial (Wiviott et al. 2006). Approximately 13,600 patients with moderate to high-risk ACS undergoing PCI (9,500 unstable angina [UA]/non-ST segment elevation MI [non-STEMI], 3,500 ST-segment elevation MI [STEMI]) were randomized to prasugrel 60 mg LD followed by 10 mg daily MD or clopidogrel 300 mg LD followed by 75 mg daily MD for up to 15 months in combination with low-dose aspirin. The primary objective was to test the hypothesis that prasugrel is superior to clopidogrel on a background of aspirin in the treatment of patients with ACS who are to undergo PCI as measured by the composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke at a median follow-up of approximately 12 months. The results of TRITON-TIMI 38 have recently been published (Wiviott et al. 2007).

Comparison with the Clopidogrel 600 mg LD

In the phase 3 TRITON trial, the approved 300 mg LD of clopidogrel was used as the comparator for prasugrel. Some institutions use a nonapproved 600 or 900 mg LD of clopidogrel during PCI procedures since it has been reported to provide more rapid and higher platelet inhibition compared with the 300 mg LD (Montalescot et al. 2006; Smith et al. 2005; Patti et al. 2005; von Beckerath et al. 2005). However, even with the higher clopidogrel 600 mg LD, there is still significant inter-individual variation in the PD response (Hochholzer et al. 2005).

A phase 1, randomized, 3-period crossover study was conducted to compare the IPA achieved in healthy, aspirin-free subjects receiving the approved clopidogrel 300 mg LD/75 mg MD, the high-dose clopidogrel 600 mg LD/75 mg MD, and the prasugrel 60 mg LD/10 mg MD dosing regimens (Payne et al. 2007). Figure 7 presents the IPA levels achieved after prasugrel or clopidogrel LDs and 7 days of daily MDs. As early as 30 min after the LDs, the prasugrel 60 mg LD resulted in a significantly higher IPA (52.1%) than either clopidogrel 600 mg LD (4.3%) or the 300 mg LD (1.3%). The maximum effect of the clopidogrel 300 and 600 mg LDs occurred approximately at 6 hours, and the corresponding IPA levels were approximately 50% and 70%, respectively, compared with approximately 90% for the prasugrel 60 mg LD. These LD effects were maintained for 24 hours. During maintenance dosing, prasugrel 10 mg maintained a significantly greater and less variable IPA than the clopidogrel 75 mg dose on all days. As found in other studies, the greater antiplatelet effect with prasugrel was shown to be related to higher levels of prasugrel’s active metabolite following both LD and MD. No serious adverse events or severe bleeding events were reported for prasugrel or clopidogrel. Mild spontaneous and minor bleeding (hematoma) at venipuncture sites were more common with the clopidogrel 600 mg LD and prasugrel 60 mg LD than with clopidogrel 300 mg LD (Payne et al. 2006).

More recently a double-blind comparison of clopidogrel 600 mg and prasugrel 60 mg has been performed in aspirin-treated patients with stable coronary artery disease (Siegbahn et al. 2007; Varenhorst et al. 2007). In large part, the observations made in healthy volunteers, as described above, were reproduced in this patient population. Thus, within 30 min of administration, prasugrel 60 mg significantly reduced maximal platelet aggregation compared with clopidogrel 600 mg, which at this early time point had no significant effect. In this setting, the maximal platelet inhibition achieved following LDs was at approximately 2 hours for either drug, at which time the level of platelet aggregation in the prasugrel group was approximately 50% lower than that in the clopidogrel group (Varenhorst et al. 2007).
In parallel with platelet aggregation studies, VASP phosphorylation was measured. VASP is a more specific test of P2Y<sub>12</sub> blockade expressed as the platelet reactivity index (PRI, %) that approximates P2Y<sub>12</sub> receptor functionality (i.e., PRI of 100% = fully functional and PRI of 0% = fully blocked). The data confirmed the aggregation data showing high grade P2Y<sub>12</sub> blockade at 1, 2, and 24 hours for prasugrel 60 mg with significantly less inhibition at corresponding time points following 600 mg clopidogrel (Siegbahn et al. 2007). Thus overall two independent studies in different populations indicate that 60 mg prasugrel provides more rapid and more potent inhibition of P2Y<sub>12</sub> and platelet aggregation than the higher clopidogrel LD of 600 mg. Presumably, this also reflects greater exposure to the active metabolite of prasugrel than to that of clopidogrel.

**CONCLUSIONS**

Prasugrel is a potent novel thienopyridine antiplatelet agent and has been shown in preclinical and clinical studies to achieve faster onset, higher levels of platelet inhibition, and less response variability than clopidogrel. This antiplatelet profile reflects more efficient generation of the active metabolite of prasugrel. In addition, preliminary data suggest that prasugrel is better tolerated than clopidogrel. The TRITON-TIMI 38 trial was a large pivotal registration trial that assessed whether prasugrel was superior to clopidogrel as measured by the composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke with acceptable safety in patients with ACS undergoing PCI.

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ADDENDUM

Chemical Names of Drugs

AZD6140 (ticagrelor): (1S,2S,3R,5S,)-3-[7-(1R,2S)-2-[3,4-difluorophenylcyclopropyl]amino]-5 (propylthio)-3H-[1,2,3]-trialzolo(4,5-d)pyrimidin-3-yl-5-[2-hydroxyethoxy] cyclopentane 1,2-diol
Cangrelor (AR-C69931MX): 5’-adenylic acid, N-[2-(methylthio)ethyl]-2-[3,3,3-triofluoropropylthio]-, monoanhydride with (dichloromethylene)bis[phosphonic acid], tetrasodium salt
Clopidogrel: (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1)
Prasugrel (CS-747, LY640315): 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, hydrochloride
Ticlopidine: 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride

Clinical Trials

CLASSICS: CLopidogrel ASpirin Stent International Cooperative Study
CREDO: Clopidogrel for the Reduction of Events During Observation
CURE: Clopidogrel in Unstable angina to prevent Recurrent ischemic Events
EXCELSIOR: impact of EXtent of Clopidogrel-induced platelet inhibition during ELective Stent Implantation On clinical event Rate
JUMBO-TIMI 26: Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis In Myocardial Infarction 26
PCI-CURE: Percutaneous Coronary Intervention- Clopidogrel in Unstable angina to prevent Recurrent ischemic Events
TRITON-TIMI 38: TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Inhibition Thrombolysis In Myocardial Infarction 38

Abbreviations

ACS: acute coronary syndrome
ADP: adenosine 5’-diphosphate
AUC: area under the time concentration curve
CABG: coronary artery bypass graft
C max: maximum concentration
CYP: cytochrome P-450
IPA: inhibition of platelet aggregation
LD: loading dose
LTA: light transmission aggregometry
MACE: major adverse cardiac events
MD: maintenance dose
MI: myocardial infarction
PCI: percutaneous coronary intervention
PD: pharmacodynamic
PRI: platelet reactivity index
SAT: stent associated thrombosis
$T_{\text{max}}$: time of maximal concentration
TRAP: thrombin receptor activating peptide
TXA$_2$: thromboxane A$_2$
VASP: vasodilator-associated phosphoprotein

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